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PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	SIEGEL, S.J.	Examiner:	FUBARA B.M.
Serial No.:	10/046,504	Group Art Unit:	1618
Filed:	October 19, 2001		
Title:	POLYMER-BASED SURGICALLY IMPLATABLE HALOPERIDOL DELIVERY SYSTEMS AND METHODS FOR THEIR PRODUCTION AND USE		

DECLARATION UNDER RULE 37 C.F.R. 1.132

Assistant Commissioner for Patents
Washington, DC 20231

I, SIEGEL, Steven, a citizen of United States of America, residing at 86 Highpoint Drive, Berwyn, PA 19312 , hereby declare:

1. I am an **Assistant Professor** at the **University of Pennsylvania**. I have an M.D. and a Ph.D. in **Biomedical Science/Neurobiology** from **Mount Sinai School of Medicine**. My fields of expertise are The Neurobiology and Pharmacology of Schizophrenia, The Clinical management of Psychotic Disorders, Electrophysiology, and Polymer based Drug Delivery. Specifically I have been involved in the study of **Clinical studies of the Biological basis of Schizophrenia, Electrophysiological evaluation of candidate genes and neural pathways responsible for the abnormal behaviors and mental processes in schizophrenia, the acute and lasting consequences of drugs of abuse including ketamine and nicotine, Novel medication treatments for**

Psychotic disorders and discovery and development of long term biodegradable polymer drug delivery systems for schizophrenia and other neuropsychiatric disorders.

2. My Curriculum Vitae and list of publications are attached herewith as Appendix 1.

3. I have read the subject Application and have reviewed the patent Prosecution History, including the Office Action of February 10, 2004, September 13, 2005, April 8, 2005, August 25, 2005 (advisory action), November 16, 2005, May 4, 2006, and October 19, 2006. The subject Application describes *inter alia*, a surgically implantable drug delivery system comprising a biodegradable polymer or copolymer selected from the group consisting of polylactide and lactide-co-glycolide copolymer and 20 to 40% haloperidol.

4. Claim 1 of the subject Application recites a surgically implantable drug delivery system, comprising:
   (a) a biodegradable polymer or copolymer, wherein said biodegradable polymer or copolymer consists essentially of polylactide or lactide-co-glycolide copolymer; and
   (b) 20 to 40% haloperidol fabricated into an individual, surgically implantable implant via solvent casting and compression molding at a temperature and pressure which allows the haloperidol-polymer material to flow into a mold for the individual, surgically implantable implant which is surgically implanted underneath the skin of a patient, delivers steady state concentrations of haloperidol to the patient for 5 months or more and is removable from the patient in the event the patient exhibits unwanted side effects following implantation

5. Claim 4 of the subject application recites a method of producing an individual, surgically implantable implant which is surgically implanted

underneath the skin of a patient for delivery of steady state concentrations of haloperidol to the patient for 5 months or more comprising:

(a) dissolving haloperidol and a biodegradable polymer consisting essentially of polylactide or lactide-co-glycolide copolymer in acetone;

(b) solvent casting the haloperidol and biodegradable polymer solution to produce a completely dry haloperidol-polymer material; and

(c) molding under compression the dry haloperidol-polymer material at a temperature and pressure which allows the haloperidol-polymer material to flow into a mold for the individual, surgically implantable implant which is surgically implanted underneath the skin of a patient, delivers steady state concentrations of haloperidol to the patient for 5 months or more, and is removable following implantation into a patient in the event the patient exhibits unwanted side effects following implantation.

6. The specification provides exemplifications of the claimed material, whereby two polymer blends, 75% polylactide with 25% polyglycolide (75:25 PLGA) and 85% polylactide with 15% polyglycolide (85:15 PLGA) are present in a combined system of release during a 5-month period. Each copolymer has a **distinctive** period of degradation, which is determined by the ratio of lactide to glycolide and the molecular weight of the resulting molecule produced (*See* e.g. Example 1). Bioactivity of haloperidol implants was demonstrated in implants made of 75:25 PLGA alone or 75:25 with 20% haloperidol (n=8) to assess the effects of implants on locomotion. Following three weeks of implantation, total distance traversed was assessed over a twenty-minute period. Implants were then removed and animals allowed to recover for 48 hours prior to retesting 20 minutes after apomorphine challenge. Moreover incorporation of other antipsychotic agents (thiothixene) and an anti-depressant (Fluoxetine), did not perform in the present system (*See* e.g. US Publication 20020179096, pp. 4, Para 30), indicating that the drug release profile is polymer and drug-specific.

7. In the Office Action dated October 19, 2006, the Examiner rejected claims 1, 3, 4, and 6-10 under 35 U.S.C. § 103(a), as being allegedly unpatentable over Mao (US Patent No. 6,166,173). The Examiner alleged that Mao disclosed: (a) biodegradable medical implant devices that incorporate 1-65% active agent; (b) that any antipsychotic drugs (e.g. clozapine, haloperidol, and risperidone) can be used; and (c) use of lactic acid copolymers. The Examiner alleged that "The difference... between Mao and the instant claims is [only] the amount of the haloperidol" (October 19, 2006 Office Action page 3, first full paragraph). Therefore, the Examiner alleged that it would have been obvious to modify the implant of Mao to arrive at the implants claimed in the subject claims.

8. It is my opinion that the Examiner is incorrect in his assertion. Mao does not disclose a surgically implantable drug delivery system comprising a biodegradable polymer or copolymer selected from the group consisting of polylactide and lactide-co-glycolide copolymer and 20 to 40% haloperidol. Likewise, Mao does not provide a credible foundation for a biodegradable polymer or copolymer, consisting essentially of polylactide or lactide-co-glycolide copolymer and 20 to 40% haloperidol fabricated into an individual, surgically implantable implant via solvent casting and compression molding at a temperature and pressure which allows the haloperidol-polymer material to flow into a mold for the individual, surgically implantable implant which is surgically implanted underneath the skin of a patient, delivers steady state concentrations of haloperidol to the patient for 5 months or more and is removable from the patient in the event the patient exhibits unwanted side effects following implantation. Further, Mao does not provide a credible foundation for the production method of the controlled release system described in amended claim 4 as shown above. Although Mao claims, as the Examiner alleges that any antipsychotic drugs (e.g. clozapine, haloperidol, and risperidone) can be used; and (c) use of lactic acid copolymers. The Examiner alleged that "The difference... between Mao and the instant claims is [only] the amount of the haloperidol" (October 19, 2006 Office Action page 3, first full paragraph), **the results clearly shows otherwise.**

9. Moreover, (a) the polymer of Mao contains phosphate ester linkages; and (b) the presence of phosphate ester linkages in the polymer of Mao alters materially the basic and novel characteristics of the invention; namely, the release rate of the implants and the ability to alter that release rate by altering the ratio between polylactide or lactide-co-glycolide copolymer. It is unplausable that polymer system containing phosphate linkages and is therefore highly polar system, will behave similar to the polylactide or lactide-co-glycolide copolymer described here. Moreover, the maximum loading obtained by Mao were of 7.6% Lidocain, a substantially lower amount than the 20-40% described in the invention.

10. Unexpectedly at high Haloperidol concentrations, matrix degradation changes and release rates are affected. As stated in the application on page 3, para. 26, higher Haloperidol loading concentration stabilizes the system, slowing the release rate. This observed phenomenon is surprising since under normal circumstances, release rate increases the higher the initial loading concentration is (*See* e.g. Menemse GümüsdereliogGlu and Günday Deniz, Journal of Biomaterials Science, Polymer Edition Volume 11, Number 10 / December, 2000, Pages 1039-1050 "Sustained release of mitomycin-C from poly(DL-lactide)/poly(DL-lactide-*co*-glycolide) films" showing that both the rate and the percentage of released MMC increased as the drug load increased from 0.5 to 2 mg MMC per 300 mg of polymer. See also, Sharma, Kuldeepak, 1987 "Mechanisms of Drug Diffusion from Polymeric Devices" Dissertation Abstracts International, Volume: 48-02, Section: B, page: 0486, showing that initial drug load, drug loading solvents and the drug polymer interactions on release of several drugs from devices comprising both hydrophilic and hydrophobic polymers affect studied showed an increase in release as the initial drug load increased.).

11. Therefore, in my opinion, Mao does not disclose a surgically implantable drug delivery system comprising a biodegradable polymer or copolymer selected from the group consisting of polylactide and lactide-co-glycolide copolymer and 20 to 40% haloperidol, nor is the disclosure credible

considering the unexpected nature of the effects of higher Haloperidol loading on the release rate. Therefore, at the time the invention was made, the results shown by Mao could not have made it obvious for a skilled practitioner that a 20–40% loading of Haloperidol in a polylactide or lactide-co-glycolide copolymer, as claimed in the subject Application would give the same or similar release rate as 7.6% Lidocain in a poly(L-lactide-co-ethyl-phosphate) matrix.

The undersigned further declares that all statements made herein of his own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made, are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 10/17/2007